REMARKS

Applicants thank the Office for the entry of the amended Title for this application. Applicants also thank the Office for the withdrawal of the previous rejections under the first and second paragraphs of 35 U.S.C. § 112, and under 35 U.S.C. 101.

Status of the Claims

Claims 1 to 12, 15, 17 to 31, 34, 35, and 38 to 43 are pending in the application. Claims 13, 14, 16, 32, 33, 36, and 37 were previously canceled without prejudice or disclaimer. Claims 1 to 8, 10 to 12, 19 to 31, 34, and 35 were previously withdrawn. Claims 9, 15, 17, 18, and 38 to 43 are currently under consideration.

Claims 9 and 18 have been amended to delete the recitation of "diabetes" without prejudice or disclaimer. Previously withdrawn claims 3, 21, 24, 27, 30, and 34 have similarly been amended to delete the recitation of "diabetes" without prejudice or disclaimer. Claims 18, 40, and 42 have been amended to delete the recitation of "or a salt thereof" without prejudice or disclaimer. Previously withdrawn claims 5, 6, 11, 12, and 19 have similarly been amended to delete the recitation of "or a salt thereof" without prejudice or disclaimer. Thus, the amendments are fully supported by the specification and add no new matter.

Rejections Under 35 U.S.C. § 103(a)

The Office has rejected claims 9, 15, 17, 18, and 38 to 43 under 35 U.S.C. § 103(a) for allegedly being unpatentable over U.S. Patent No. 6,165,733 ("the '733 patent"), in view of Ihara et al. (August 2001, *Diabetologia*, 44(sup1):A120) ("Ihara"). Specifically, the Office maintains that:

> The '733 patent teaches a screening method for a therapeutic substance (a mitogenesis inhibitor) comprising cultivating a cell (the contacted cell had to have been "cultivated") and comparing the expression of a gene in the presence or absence of a test compound (see particularly Claims 1 and 2). While the reference does not specifically teach the comparison of mRNA expression of Claim 18, comparisons of gene expression comprise either comparisons of DNA or mRNA expression such that either are readily envisioned as equivalents.

Office Action at page 2. The Office acknowledges that the '733 patent "differs from the claimed invention in that it does not teach comparing the expression of a gene encoding the protein of SEQ ID NO:2." *Id.* However, the Office maintains that:

> Ihara et al. teaches the protein of SEQ ID NO:2 (TSC-22), is associated with diabetes. In particular, the expression of the gene of SEQ ID NO:1 can be used as a marker for insulin expression. TSC-22 inhibits insulin expression such that a measure of TSC-22 expression can be used as a measure of insulin expression and the reduction of TSC-22 expression is an indication of increased insulin expression.

Office Action at the paragraph bridging pages 2-3.

The Office thus concludes that:

> It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to employ the screening method of the '733 patent employing the measuring of the expression of the TSC-22 gene of Ihara et al. given the relationship of TSC-22 expression and insulin expression. Said method could be used as a method for screening test substances for their effect on TSC-22 expression as a measure of their efficacy as a therapeutic for the treatment of diabetes.

Office Action at page 3.

The Office acknowledges the previous arguments put forth by the Applicants in which the Applicants maintained that Ihara teaches that TSC-22 is associated with suppression of insulin gene expression, whereas the instant invention teaches the

opposite (i.e., that TSC-22 is associated with increased insulin gene expression). In response, the Office argues that:

> Regardless of the fact that the reference describes an effect opposite of that described in the instant specification the combined references still provide a reason for assaying the effect of candidate drugs on the TSC-22/insulin pathway. There is no necessity that the motivation or findings of the prior art be identical to that of the instant Inventors.

Office Action at page 3. Applicants respectfully disagree.

The Office also acknowledges the previous arguments by the Applicants in which the Applicants maintained that Sugawara et al. (2001, *Intern Med* 40(10): 993-997) ("Sugawara"), teaches away from Ihara. With regard to the previous work of Ihara, the Office provides a quote from Sugawara stating:

> [In unpublished work by Ihara Y.,] [w]e found that the expression of TSC-22 gene is increased in the pancreatic islets of an eight-week-old male GK rat, compared to the islets from a control male Wistar rat, in a differential display. . . . Furthermore, we found that the human insulin gene promoter activity was repressed by the TSC-22 gene product, (page 993).

Office Action at page 3. However, the Office contends that the more recent work of Sugawara "concerned the question of whether specific SNPs (single nucleotide polymorphisms) [in TSC-22] correlated with type 2 diabetes. The finding was that they did not." *Id.* Although Sugawara did not identify an association between SNPs in TSC-22 and type 2 diabetes and states in the abstract that "[i]t is unlikely that the TSC-22 gene is a locus responsible for type 2 diabetes," the Office maintains that "[t]his finding in no way teaches away from the findings of Ihara et al." *Id.* Applicants respectfully disagree.

Contrary to the contentions of the Office, Applicants maintain that it would not have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the screening method of the '733 patent with the teaching of Ihara regarding the relationship between TSC-22/insulin expression, to yield the screening method of the instant invention for the identification of prophylactic or therapeutic substances for renal disease. Applicants assert that all of the claim limitations are neither taught nor suggested by the '733 patent and Ihara, and that even when combined, the '733 patent and Ihara do not yield the claimed invention.

The instant claims recite a screening method for a prophylactic or therapeutic **substance that "changes the expression level** of the insulin gene or [a] gene under the control of the insulin promoter" (claim 9) or that "**changes the expression level** of" an mRNA that encodes a protein comprising the same or substantially the same amino acid sequence as the amino acid sequence shown by SEQ ID NO: 2 or a partial peptide thereof (claim 18). In contrast, the '733 patent teaches a screening method for substances that "inhibit the interaction of γ II adaptin and phosphatidylinositol 3-kinase," rather than substances that affect the expression level of a gene. The '733 patent, col. 5, lines 3-5. Whereas the claimed invention is directed to the identification of prophylactic or therapeutic substances that change gene expression, the '733 patent is focused on a screening method for agents that inhibit a protein-protein interaction.

Indeed, the '733 patent discloses and claims the use of a "two-hybrid assay . . . to assay for useful agents for inhibiting the interaction between γ II adaptin and phosphatidylinositol 3-kinase." The '733 patent, col. 5, lines 25-27. Specifically, the '733 patent states that:

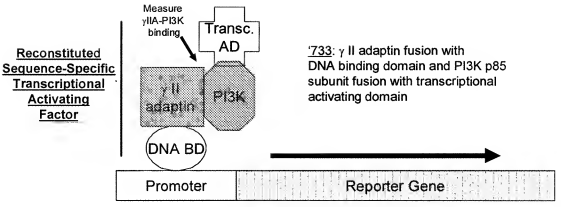
> The basis for all of these assays is the discovery of the binding interaction between γ II adaptin and phosphatidylinositol 3-kinase, and the functional consequence of the binding in mediation of the intracellular signaling of P[DG]F. Since P[DG]F is a known mitogen, **agents which are found to inhibit the interaction of γ II adaptin and phosphatidylinositol 3-kinase will be useful in inhibiting mitogenesis**.

The '733 patent col. 4, line 65 to col. 5, line 5 (emphasis added). Thus, a protein-protein interaction (between γ II adaptin and phosphatidylinositol 3-kinase) serves as the basis for the screening method of the '733 patent, and a substance capable of inhibiting that protein-protein interaction is the target of the screening method.

The '733 patent describes the utility of the two-hybrid system as follows:

> According to such an assay, fusion proteins of each of the binding partners are used which each contain at least the domains necessary for the binding interaction. One of the binding partners is fused to a DNA binding domain and the other is fused to a transcriptional activating domain. **The two proteins interact to reconstitute a sequence-specific transcriptional activating factor.** The two fusion proteins are produced in a cell which also contains a reporter gene which is sensitive to the activation of the reconstituted sequence-specific transcriptional activating factor. In the absence of a test compound the cell expresses the reporter gene. Test compounds are added to the cell and the effect on the reporter gene's expression is monitored. **A test compound which disrupts the binding of the γ II adaptin and phosphatidylinositol 3-kinase domains will have a negative effect on the transcriptional activation ability of the reconstituted sequence-specific transcriptional activating factor. Thus the expression of the reporter gene will be reduced.**

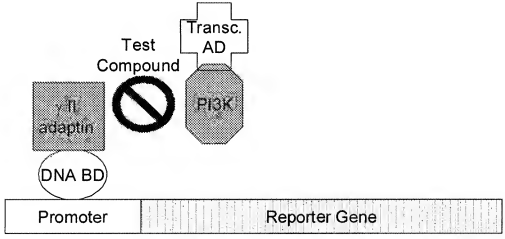
The '733 patent, col. 5, lines 27-45 (emphasis added). Thus, the '733 patent teaches a method of screening that requires two different proteins as illustrated below.



In the illustration of the method of the '733 patent above, the first protein is fused to a heterologous DNA binding domain, and the second protein is fused to a heterologous transcriptional activating domain. The DNA binding domain and the transcriptional activating domain are merely used as a means to detect protein-protein interactions and can be fused to any proteins that have the potential to interact with each other. Thus, in the real world, the functions of the DNA binding domain and the transcriptional activating domain are independent of the functions of the proteins fused to them. When the fused proteins (e.g., γ II adaptin and PI3K p85) bind to each other, they bring the DNA binding domain and the transcriptional activating domain in close enough proximity to each other to reconstitute a sequence-specific transcriptional activating factor, which leads to the expression of a reporter gene. It is the DNA binding domain in this reconstituted transcriptional activating factor that binds to the promoter. The '733 patent, col. 3, lines 6-8 (the reporter gene comprises "a DNA sequence to which the DNA binding domain of the first fusion protein specifically binds."). Reporter gene expression levels in the two-hybrid assay simply indicate the strength of the protein-protein interaction between the protein fused to the DNA binding domain and the

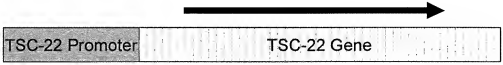
protein fused to the transcriptional activating domain and do not provide any information regarding the function of the fused proteins on gene expression.

Thus, as shown below, when a test compound is added and disrupts the binding between the fused (e.g. γ II adaptin and PI3K p85) proteins, the transcriptional activating factor fails to reconstitute and fails to initiate gene expression because the DNA binding domain and the transcriptional activating domain are not brought into close proximity of each other. The test compound can be said to be an inhibitor of the protein-protein interaction, but nothing can be said about its usefulness as an agent for altering gene expression.

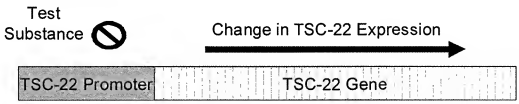


Accordingly, the two-hybrid method of the '733 patent would not be useful for identifying a prophylactic or therapeutic substance that "**changes the expression level** of the insulin gene or [a] gene under the control of the insulin promoter" or that "**changes the expression level** of the mRNA that encodes" a protein comprising the same or substantially the same amino acid sequence as the amino acid sequence shown by SEQ ID NO:2 (TSC-22) or a partial peptide thereof as recited in the claims.

For example, independent claim 18 is directed to the regulation of the expression of SEQ ID NO:2 (TSC-22) (or a protein comprising substantially the same amino acid sequence as SEQ ID NO:2 or a partial peptide) as illustrated below:



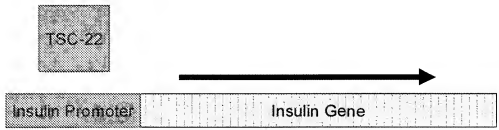
A candidate for a prophylactic or therapeutic substance for renal disease is a test substance that alters the expression level of TSC-22:



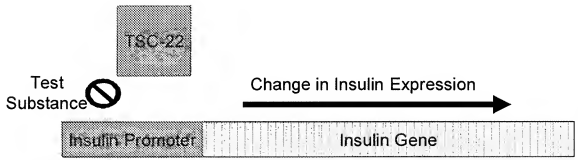
The method of claim 18 does not require two proteins that are capable of binding to each other. In contrast, and as discussed above, the screening method of the '733 patent does require at least two proteins that are capable of binding to each other. However, neither the '733 patent nor Ihara teach or suggest two proteins that may be useful for identifying a test substance that alters the expression level of TSC-22. Moreover, the '733 patent nor Ihara teach how two proteins can be useful for identifying a substance that alters the expression level of TSC-22.

The two-hybrid assay of the '733 patent also would not be useful for identifying a prophylactic or therapeutic substance that "changes the expression level of the insulin

gene or [a] gene under the control of the insulin promoter" as recited in independent claim 9. An embodiment of the method of claim 9 may be illustrated as follows:



TSC-22 may bind to the insulin promoter and initiate insulin gene expression. A candidate for a prophylactic or therapeutic substance for renal disease is a test substance that alters the expression level of the insulin gene (or a gene under the control of the insulin promoter):



In this instance, the TSC-22 protein may potentially serve as the first protein in a two-hybrid assay, or as a protein that interacts with the insulin promoter. Ihara does disclose that "-170 to -88 of the insulin promoter was important for interaction with TSC-22." Ihara, second to last sentence. However, neither the '733 patent nor Ihara teach or suggest a second protein capable of interacting with TSC-22. Moreover, even if a second protein were identified, neither the '733 patent or Ihara teach how it may be

used to identify a test substance that alters the expression level of the insulin gene or a gene under the control of the insulin promoter. Thus, the combination of the '733 patent together with Ihara does not yield the claimed invention.

Not withstanding the inapplicability of the screening method of the '733 patent to the claimed invention, Ihara does not teach or suggest an association between TSC-22 and renal disease or diabetic nephropathy. Rather, Ihara is focused exclusively on the identification of TSC-22 as a potential candidate gene for type 2 diabetes. Indeed, the Goto-Kakizaki (GK) rat model employed by Ihara is a model of non-obese type 2 diabetes that is not widely considered a model of diabetic nephropathy, because GK rats exhibit a late onset of symptoms associated with diabetic nephropathy (i.e., at 24 months of age). *See* Sato et al. "Late Onset of Diabetic Nephropathy in Spontaneously Diabetic GK Rats," *Am J Nephrol* 23:334–342 (2003), at page 334 (abstract), and at the paragraph bridging pages 340-341 (copy enclosed with concurrently filed IDS). Ihara examined TSC-22 expression levels in 8-week-old GK rats, which would be far before the rats develop any symptoms of diabetic nephropathy. In contrast, the instant invention discloses the use of three different rat models of renal disease, including diabetic nephropathy, and examines TSC-22 mRNA expression levels in kidney tissue. Specifically, the instant invention examined TSC-22 mRNA expression levels in: 1) Wistar fatty rats, which have non-insulin-dependent diabetes (NIDDM) and spontaneously develop diabetic nephropathy (Example 1), 2) Zucker fatty rats, which have hyperinsulinemia and spontaneously develop renal disease (Example 2), and 3) spontaneously hypercholesterolemic (SHC) rats, which are hypercholesterolemic and spontaneously develop renal disease (Examples 3 and 4). Further, Example 2 of the

instant invention shows that treatment of SHC rats with candesartan cilexetil, which suppresses the increase in urinary albumin excretion in SHC rats, was accompanied by a decrease in the upregulation of TSC-22 mRNA expression levels relative to vehicle-treated control SHC rats.

Applicants respectfully assert that the deficiencies of the '733 patent and Ihara are such that even when combined, they fall short of yielding the claimed invention. Based on these deficiencies, one of skill in the art would not have been motivated and would not have had a reason to combine the teaching of the '733 patent with that of Ihara to arrive at the instant invention. Accordingly, Applicants respectfully request withdrawal of the rejection.

Rejections Under 35 U.S.C. § 112, First Paragraph

The Office has rejected claims 38[1] and 42 under 35 U.S.C. § 112, first paragraph, for allegedly not containing a written description of the claimed invention. The Office asserts that "the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed." Office Action at page 4. The Office states that this is a "written description rejection for the introduction of new matter into the claims." *Id.* Specifically, the Office alleges that "[t]he specification and the claims as originally filed do not

[1] Although the Office Action at page 4 states that claims 38 and 42 are rejected under U.S.C. § 112, first paragraph, claim 38 does not recite "wherein the cell has the ability to produce a protein comprising the amino acid sequence shown by SEQ ID NO:2 or a salt thereof." We believe that the Office instead meant to reject claim 40, which previously recited "wherein the cell has the ability to produce a protein comprising the amino acid sequence shown by SEQ ID NO:2 or a salt thereof," instead of claim 38.

provide support for the invention as now claimed, specifically, a method wherein the cell employed in the assay has the ability to produce the protein of SEQ ID NO:2." *Id.* Applicants respectfully disagree.

Support for use of a cell that has the ability to produce the protein of SEQ ID NO:2 can be found throughout the specification, for example, at p. 9, lines 17-20; p. 25, lines 9-12; p. 28, lines 29-31; and p. 33, line 17 - p. 34, line 5. Therefore, Applicants respectfully request withdrawal of the rejection.

Rejections Under 35 U.S.C. § 112, Second Paragraph

The Office has rejected claims 38[2] and 42 under 35 U.S.C. § 112, second paragraph, as allegedly "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, specifically, the recitation of a cell that produces a salt of the protein of SEQ ID NO:2 is nonsensical as cells do not produce proteins of salts." Office Action at page 4. Applicants respectfully disagree.

Nevertheless, without conceding to the rejection and in an effort to advance prosecution, Applicants have deleted "or a salt thereof" from the claims without prejudice or disclaimer. Accordingly, Applicants respectfully request withdrawal of the rejection.

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[2] Although the Office Action at page 4 states that claims 38 and 42 are rejected under U.S.C. § 112, second paragraph, claim 38 did not previously recite "wherein the cell has the ability to produce a protein comprising the amino acid sequence shown by SEQ ID NO:2 or a salt thereof." We believe that the Office instead meant to reject claim 40, which previously recited "wherein the cell has the ability to produce a protein comprising the amino acid sequence shown by SEQ ID NO:2 or a salt thereof," instead of claim 38.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request the Office's reconsideration and reexamination of the application, and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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Dated: June 3, 2009

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